Response to Comments on Final Public Review Draft Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

July, 2001

Response to Comments on Methylene Chloride by Paul Dugard (HSIA)

The Halogenated Solvents Industry Alliance (HSIA) submitted comments in response to the notice regarding the prioritization of the Toxic Air Contaminants (TACs) for the California Children's Environmental Health Protection Act (SB25) in a letter from Dr. P.H. Dugard dated July 13, 2001.

Comment 1: Carboxyhemoglobin in the fetus following maternal exposure to methylene chloride could arise from carbon monoxide released by maternal metabolism that reaches the fetal blood, or by metabolism of methylene chloride in fetal tissues. Neither source is likely to contribute to COHb in fetal blood such that the level is above, or even reaches, that in the maternal system.

Response 1: OEHHA agrees that at current ambient levels methylene chloride does not significantly contribute to carboxyhemoglobin levels in fetuses, infants or adults. However, although methylene chloride levels in fetal blood following maternal exposure tend to be lower than those in maternal circulation, carbon monoxide levels in fetal blood do reach levels comparable to maternal blood (Anders & Sunram, 1982). In addition, the fetal capacity to dissociate carboxyhemoglobin and convert CO to CO_2 is lower than in adults.

Comment 2: It should be noted that the metabolism of methylene chloride by P450 enzymes is saturable; this limits the maximum rate of production of carbon monoxide and gives a ceiling to the level of COHb that can occur from exposure to methylene chloride (Andersen et al., 1991). This means that severe carbon monoxide poisoning cannot occur as a result of exposure to methylene chloride.

Response 2: In the experiments reported by Andersen et al (1991) a peak COHb level of 8% was achieved in humans following exposure to methylene chloride at 2,000 ppm for 3 hours. A similar COHb level (9%) was reported by Longo (1970) to be equivalent to a 41% reduction in fetal blood flow or in fetal hemoglobin concentration. Thus while this high level of methylene chloride is unlikely to be encountered except during accidental exposure, this work underscores that for the fetus the consequences of maternal exposure are serious and include not just the formation of fetal COHb, but also a reduction in the oxygen available from maternal circulation. Elevated maternal COHb has been associated with reduced birth weights it humans (Astrup et al., 1972; Longo, 1977), and is thought to contribute to the lower birth weights associated with maternal exposure to methylene chloride during pregnancy in rats (Hardin and Manson, 1980).

Comment 3: None of the factors contributing to the prioritization process, exposure patterns among infants and children that result in disproportionately high exposure; special susceptibility of infants and children; effects of simultaneous exposure to

compounds with the same mechanism of action; any interactions of air pollutants, supports the prioritization of methylene chloride as a Tier 2 substance.

Response 3: The available data suggest that there is a differential susceptibility of children and fetuses to methylene chloride compared to adults. The CO formed after exposure to methylene chloride is bound with greater affinity by fetal hemoglobin, and fetuses and infants are less able to enzymatically eliminate COHb. In addition, the developing fetal nervous system is expected to be more sensitive to hypoxia associated with COHb formation. However, due to its low ambient levels and relatively low toxicity, methylene chloride was not included in Tier 1 and no further action is required or anticipated under this process at this time. Nevertheless, we will keep these comments in mind if future review becomes necessary.

Anders and Sunram. 1982. Transplacental passage of dichloromethane and carbon monoxide. Toxicol Lett 12, 231-4.

Andersen et al. 1991. Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. Toxicol Appl Pharmacol 108, 14-27.

Astrup et al. 1972. Effect of moderate carbon-monoxide exposure on fetal development. Lancet 2, 1220-2.

Hardin and Manson. 1980. Absence of dichloromethane teratogenicity with inhalation exposure in rats. Toxicol Appl Pharmacol 52, 22-8.

Longo. 1970. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann NY Acad Sci 174, 312-41.

Longo. 1977. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol 129, 69-103.